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Diagnosis, epidemiology, assessment, pathophysiology, and management of fetal alcohol spectrum disorders

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Abstract

Prenatal alcohol exposure (PAE) frequently causes neurodevelopmental disorder, yet fetal alcohol spectrum disorders (FASD) are often undiagnosed. Global prevalence rates of 0.77% for FASD and European / North American rates of 2–5% highlight the need for neurologists to engage in identification, assessment, and treatment of this preventable disorder. Diagnosis remains challenging because of limitations of self-report of drinking, lack of biomarkers, and infrequency of diagnostic dysmorphic facial features. Multiple diagnostic systems and disagreement over diagnostic criteria have slowed progress in the field. PAE impacts neurodevelopment through diverse mechanisms including oxidative injury, apoptosis, modulation of gene expression, and disruption of neuronal migration / axon pathfinding. Neuroimaging reveals abnormal brain structure, cortical development, white matter microstructure, and functional connectivity. These abnormalities modify developmental trajectories and are associated with deficits in cognition, executive function, memory, vision, hearing, motor skills, behavior, and social adaptation. Trials of promising nutritional interventions and cognitive rehabilitation are underway.

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Contributions

All three authors contributed equally to the conceptual development, literature review, and the drafting and revision of this paper. All three authors have given final approval of the submitted version and agree to be held accountable for all aspects of the work.

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Introduction

FASD is an encompassing term covering a range of conditions related to gestational alcohol exposure, including minor craniofacial anomalies, growth retardation, neurological abnormalities, cognitive and behavioral impairment, and birth defects.[1] FASD results from PAE and affects 0·77% of the global population and 2·0 – 5·0% in Europe and North America, with variation by country and epidemiological method.[2,3] The high public health burden of FASD includes lifelong physical and cognitive disability, behavioral disturbance, psychiatric and medical comorbidity, diminished productivity, unemployment, homelessness, and incarceration.[4] Although FASD is as common as autism spectrum disorder, it remains under-diagnosed, likely due to social stigma, complexity of diagnosis, reliance on facial features, and overlap with alternative diagnoses, such as Attention Deficit Hyperactivity Disorder (ADHD). Many individuals with milder FASD have subtle neurodevelopmental effects that do not prompt clinical attention. Recent efforts to improve identification and management of FASD include studies in non-clinically-referred groups, studies of school-based populations, international studies examining high risk populations, advanced 3D imaging of facial characteristics, and new neurobehavioral screening tools.

We provide a review for neurologists of recent FASD research, beginning with an outline of the epidemiology and clinical features. We describe brain anomalies in FASD and review their underlying pathophysiology. We discuss several diagnostic systems, the developmental course, and the management of FASD. Although FASD is typically encountered during childhood, we include a discussion of issues relevant to adults with FASD, because the clinical manifestations persist into adulthood[4], and adult neurologists are often unfamiliar with FASD.

PAE often occurs in the context of polysubstance use, further complicating neurodevelopmental outcomes. However, because PAE alone may cause FASD[5] and PAE poses more severe risks to neurodevelopment than tobacco, cannabis, methamphetamine and other drugs[6], this review focuses on the developmental consequences of PAE.

Epidemiology

The global prevalence rates of Fetal Alcohol Syndrome (FAS) and the full spectrum of PAE-related conditions were estimated in a meta-analysis to be 0·15% and 0·77%, respectively. There are large regional differences, with FAS as high as 11·1% in South Africa[3] and low rates in countries with religious prohibitions against alcohol. Rates in sub-Saharan Africa are mostly unknown but believed to be high based on the frequency of binge drinking[7]. High rates, including estimates of 4·1% to 4·7% for Italy, have been challenged as unreliable[8] but are generally seen as the best available indicators, despite limitations. Variability in regional estimates of FAS and FASD reflects differences in epidemiological methodology, definitions of FAS and FASD, and regional patterns of drinking during pregnancy as well as associated risk factors including maternal nutrition and prenatal care. One recent large study in the United States (US) utilized active case ascertainment (identifying cases in a non-clinical group such as an entire school district), maternal interviews, dysmorphology exams, and neurobehavioral testing to estimate FASD prevalence in first graders across four regions.[2]

Among 222 children classified with FASD, only two (<1%) had been diagnosed previously, confirming that FASD is an often overlooked public health concern.[9,10] The prevalence of FASD across sites ranged from 1·1 to 5·0%, including 0 to 0·78% for FAS (27 children), 0·84 to 5·9% for partial FAS (pFAS) (104 children) and 0·9–5·0% for alcohol-related neurodevelopmental disorder (ARND) (91 children) (3.4 cases of ARND for every case of FAS).

High FASD prevalence reflects the high prevalence of alcohol use and PAE: approximately 25% of 18–34 year old men and women binge drink (defined by NIAA as five of more drinks per occasion for men and four or more for women),[11] and 7·3% of pregnancies are alcohol-exposed.[12] Approximately 45% of pregnancies are unplanned,[13] and many are unrecognized during the first days after the first missed menstrual period, when disruption of gastrulation and neurulation by alcohol may result in the cardinal craniofacial features and brain abnormalities of FAS.[5,14] Most concerning, binge drinking by women of childbearing age remains a problem globally and is increasing in some countries.[15]

FASD is a preventable condition that can be addressed through public health efforts, including supporting timely abstinence from alcohol, alcohol abuse prevention, addiction treatment, and birth control. Since the 1980's, women who are pregnant or trying to conceive have been advised against drinking alcohol.[16] Research over four decades in animals and humans has not established a safe level of PAE,[17] leading to warning labels on alcoholic beverages and formal recommendations by governments and professional organizations to avoid PAE (Side panel #1).

The public health impact of FASD is amplified by significant neuropsychiatric and medical co-occurring / co-morbid conditions. Meta-analyses examining FASD cohorts have revealed marked increases in behavioral disturbance, (e.g. ADHD : 8 to 10-fold increase over population prevalence rates in the literature and published by the U.S. National Institutes of Health), language disorder (10-fold), intellectual impairment (97-fold), psychosis (24-fold), anxiety disorders (11-fold), otitis media (7-fold), and conductive or sensorineural hearing loss (126 to 129-fold).[18,19] Animal studies suggest a role for PAE in the developmental origins of health and disease – including immune dysfunction, metabolic disorder, endocrine disturbance, and obesity,[20,21] although these conditions clearly have multiple etiologies. Studies of individuals clinically diagnosed with FASD have some inherent bias, because treatment-seeking individuals have more medical, cognitive, and behavioral problems than non-treatment seeking individuals. An example of this bias is the high rate of comorbid ADHD (48%) observed in a clinic-referred sample of children with FASD compared to the rate seen in a prospective cohort (8.7%).[22] Alternative designs, such as the prospective cohort design used in the Safe Passage study of 12,000 pregnancies in South Africa and the United States[23] and the retrospective cohort used in the United Kingdom's Millennium Cohort Study of more than 18,000 mother-child pairs[24] complement studies of treatment-seeking individuals. For example, the Millennium Cohort Study found no relation between PAE and autism, an important observation given previous suggestions of overlap between the two disorders.[25]

Clinical Features

Dysmorphology

The clinical recognition of craniofacial dysmorphology in FASD - most commonly short palpebral fissures, smooth philtrum, and thin upper lip vermilion - is important, because it may narrow the differential diagnosis in the presence of developmentally related brain abnormalities, neurocognitive deficits, behavioral abnormalities, and/or a history suggesting PAE. However, dysmorphic features (typically evaluated by dysmorphologists, clinical geneticists, and pediatricians) are clinically detectable in a minority of cases. The number of individuals with FASD greatly exceeds the capacity of specialists and FASD clinics.[26]

Clinicians should be aware of several minor physical anomalies that are observed frequently in individuals with PAE: “railroad track” ears, ptosis, epicanthal folds, anteverted nares, midface hypoplasia, joint contractures, camptodactyly, and altered palmar creases.[27] None of these is diagnostic of FASD, but the number of minor anomalies correlates with the magnitude of PAE.[1]

Sensory and neuropsychological abnormalities

PAE impacts brain regions and sensory neurons involved in odor and taste perception. Impaired odor identification has been reported in children with FASD.[28] Animal models show reduced taste nerve sensitivity to ethanol.[29] In young adults, the relative pleasantness of alcohol odors is proportional to the magnitude of PAE.[30] This prenatal priming for alcohol could contribute to the increased risk of alcohol use disorder in those with FASD.

The eye is affected by PAE through direct toxicity and loss of the normal inductive effect of adjacent brain on eye development. In humans, PAE may cause microphthalmia with associated reduction in palpebral fissure length, coloboma, optic nerve hypoplasia, retinal dysplasia, retinal vascular tortuosity, convergent strabismus, and low visual acuity. Ocular abnormalities may be asymmetrical.

Hearing, speech, and language disorders are more prevalent in FASD than in general pediatric populations.[18,31] Several forms of hearing loss have been reported: conductive (perhaps secondary to otitis media), sensorineural, and central. Atypical auditory processing has also been observed.[32] These impairments may have greater impact on speech, language, reading, and writing development in FASD because of co-morbid neurocognitive deficits that also impact acquisition of these skills.

Developmental delay in FASD may be detectable during infancy,[33] but a single assessment is insufficient, because neurobehavioral impairments manifest differently across the lifespan, and the sensitivity of different assessments varies with age. Cognitive impairment ranges from profound intellectual impairment to selected deficits in attention, executive functioning, memory, visual-perceptual / visual-motor skills, and academic performance[34] that may be present even when physical characteristics of FASD are absent (e.g. in ARND).[35] Similarly, adaptive functioning and social skills may be affected disproportionately in FASD, potentially reducing the capacity for independent living.[36] Disorders of behavioral and emotional regulation are common and functionally disabling. Hyperactivity, poor

impulse control, aggression, and poor social skills compromise school and workplace performance and may lead to criminal justice involvement.[4] Adverse social outcomes may also reflect the chaotic social circumstances of many individuals with FASD: multiple foster homes; violence; physical and sexual abuse; and poverty. In summary, a history of PAE should trigger a comprehensive neuropsychological evaluation of IQ, attention, executive functioning, memory, and visual-motor coordination as well as a detailed mental health assessment. Efforts to streamline the neurocognitive evaluation of FASD[37] have not yet identified a highly specific "signature", but may eventually increase the simplicity and efficiency of this important component of the diagnosis.

Neurological deficits

A careful history, including questions about maternal substance abuse, may reveal PAE, but this information is often unavailable or unreliable. The neurological exam may show non-specific findings, including cranial nerve abnormalities, dysarthria, hypotonia, reflex changes, and limb and gait ataxia.[38,39] Visual impairment may be associated with optic nerve hypoplasia and tortuosity of the retinal vessels,[40] and hearing impairment may be detected. Infants may be delayed in walking, and gross motor deficits (balance and incoordination) may be noted. These deficits occur with increased frequency in children with heavy PAE, although precise prevalence is unknown.[41] Likewise, fine motor deficits are more common in children with FASD.[42]

Fine and gross motor deficits are frequently identified using standardized tests conducted by psychologists, physical therapists, and occupational therapists.[41] Children with PAE have larger foot angles, increased step width, and greater gait variability than controls.[43] Children with FASD also have lower fine motor composite scores and manual coordination scores as well as poorer graphomotor skills (excessive handwriting pressure and an increase in cross-thumb grasping style). These deficits may limit children with FASD in performing basic motor skills in everyday life.

Co-morbidities / co-occurring conditions

Epilepsy rates of 5·9% have been reported in FASD compared to 0.5% in the general population,[18] and a prospective study of 5 to 16 year-old international adoptees with FASD found seizures or abnormal EEG in 24·6% of cases.[44] The authors highlighted the occurrence of electrical status epilepticus during sleep in one patient and referenced two similar cases of this rare condition in children with FASD. Malformations of cortical development, such as heterotopias or polymicrogyria, may contribute to epilepsy in FASD.[45] Likewise, copy number variation or hypermethylation of cytosine-guanine dinucleotide sites in genes associated with neurodevelopmental disorder and epilepsy may play a role.[46,47]

Sleep disturbances occur frequently in FASD and may contribute to the neurocognitive and behavioral deficits.[48] Clinical assessment and polysomnography identified sleep disorders - most previously undiagnosed - in 58% of children and adolescents from an FASD clinic compared to 20–30% in this age range in the general population.[49] Insomnia and parasomnias were observed most frequently, followed by diminished sleep efficiency and sleep fragmentation. Almost 80% had an anomalous melatonin profile. Sleep disturbances in

FASD result from abnormalities in central respiratory modulation, upper airway obstruction, disruption of Period genes and circadian rhythms, and damage to the suprachiasmatic nucleus and associated sleep neural circuitry.[48,50]

Brain Abnormalities

The effects of alcohol on diverse developmental events account for the wide variety of neuropathological abnormalities observed following PAE. A recent MRI study of Russian adoptees with FASD observed hypoplasia of the corpus callosum and cerebellum, vascular anomalies, focal gliosis, perivascular space dilation, pituitary hypoplasia, ventriculomegaly, cavum septum pellucidum, and simplified gyral pattern.[51] A neuropathological study of 174 individuals with FASD or a history of heavy PAE revealed similar abnormalities as well as microcephaly, neural tube defects, holoprosencephaly, and other defects.[52] Findings among a subgroup of 65 infants who died within the first year included microencephaly in 31 (13%), dysgenesis of the posterior corpus callosum in five (8%), and minor heterotopias in four (6%). By comparison, MRI studies of nearly 5000 typically developing children detected heterotopias in approximately 0·5% and partial agenesis of the corpus callosum in 0·05%.[53,54] Many more individuals without gross neuropathological abnormality are presumed to harbor more subtle neuropathological abnormalities. The range of neuropathological findings reflects variability of timing and dose of alcohol exposure, nutritional factors, genetics, and other comorbid substance abuse. For example, alleles of the alcohol dehydrogenase gene ADH1B that accelerate alcohol metabolism also mitigate alcohol teratogenicity, likely by reducing blood alcohol concentration.[55]

Clinical imaging studies do not commonly detect gross brain abnormalities in FASD, and clinical MRI is typically insensitive in detecting the more common, subtle brain dysmorphology that gives rise to neurobehavioral dysfunction. However, clinical imaging may be indicated to rule out other structural or developmental disorders. Research studies and clinical case series have revealed a range of low prevalence gross neuroanatomical abnormalities in humans, including heterotopias, dysgenesis of the corpus callosum, cavum septum pellucidum, cerebellar dysplasia, and brainstem anomalies.[56] Advanced research MRI methods have detected selected areas of cortical thinning[57] and thickening[58] in children with FASD. Likewise, group comparisons have revealed regional alterations in total grey matter density and volume reductions in the frontal, temporal, and parietal lobes, corpus callosum, basal ganglia, thalamus, cerebellum, and amygdala, even after correcting for overall reductions in brain volume.[59] Longitudinal MRI studies of children with FASD show altered trajectories of cortical volume change, highlighting the prolonged impact of PAE on the course of postnatal development.[60]

Diffusion tensor imaging (DTI) in FASD has demonstrated microstructural white matter pathology not apparent with macrostructural MRI (Figure 1). White matter microstructural integrity in the cerebral peduncles is atypical in FASD and is correlated with eyeblink conditioning (a sensitive marker for PAE).[61] Task-based functional MRI (fMRI) has revealed numerous processing deficits in FASD including aberrant frontal-parietal functional connectivity during a spatial working memory task[62] and abnormal parietal activity during a number processing task.[63] Studies examining fMRI signal during the resting-state

characterize efficiency of functional brain networks. Significant connectivity inefficiencies are observed in children with FASD,[64] and some specific networks abnormalities correlate with white matter microstructural integrity and PAE dose.[65]

Diagnosis / Classification

There are multiple FASD diagnostic/classification systems, each with different criteria that generally address four domains: level of PAE, growth impairment, dysmorphic facial features, and neurodevelopmental abnormalities. Commonly used systems include the FASD 4-Digit Diagnostic Code[66], the Institute of Medicine (IOM) criteria – revised by Hoyme[1], the Canadian Guidelines[67], and the Centers for Disease Control (CDC) guidelines.[68] The systems are discrepant in many respects: the Hoyme criteria require only two facial features compared to three required by other systems; the Canadian system does not incorporate growth retardation as a criterion, whereas the others do; The CDC criteria are not specific regarding levels or types of cognitive impairment, whereas other systems are. Coles et al.[69] compared 1581 individuals using five diagnostic systems. Despite “fair” to “moderate agreement”, there was substantial variability in the presenting phenotype.

The available diagnostic systems each have unique merits, and the authors do not endorse any one specific system. Here we describe in detail the FASD nomenclature used by the Collaboration on FASD Prevalence (CoFASP)[1] consortium to help the reader connect recent epidemiologic data with one method of FASD classification. Table 1 shows the CoFASP diagnostic criteria for the four FASD sub-types originally delineated by the IOM[1]: FAS, pFAS, ARND, and alcohol-related birth defects (ARBD).

Through a consensus process, CoFASP set the PAE criterion at six or more drinks per week for two or more weeks during pregnancy, three or more drinks per occasion at least twice during pregnancy, or documented social / legal problems related to alcohol in proximity to the index pregnancy. This threshold is lower than for other diagnostic systems and does not meet the NIAAA threshold for a “binge” drinking episode. The NIAAA binge drinking definition was based on the risk for accidents, injuries, organ toxicity, and alcohol use disorder; however, human and animal data suggest that alcohol disrupts development at lower levels of drinking. Although FASD is most readily diagnosed following levels of PAE attained from binge drinking, lower levels of PAE may cause more subtle effects. For example, in a prospective cohort study initiated during pregnancy, Day et al.[70] demonstrated an association between one alcohol drink per day (in any trimester) and behavioral problems in offspring at age 22. Also, the Growing up in New Zealand cohort study demonstrated measurable differences in parent-reported infant temperament (but not two-year old behavior) after PAE of three drinks per week early in gestation and parent-reported behavioral effects at age two after four or more drinks per week.[71] A history of PAE is not required to diagnose FAS when the cardinal facial features (described below) are present, because of their relative specificity. In the small number of cases with atypical facial features, other causes of facial anomalies, such as genetic disorders or fetal hydantoin syndrome, should be ruled out with appropriate referrals and testing.[27,72]

Using CoFASP criteria as an example, FAS (ICD10 - Q86.0) requires craniofacial anomalies, growth retardation, abnormal brain structure / function, and neurobehavioral impairment. The exam must reveal at least two of the three cardinal craniofacial features from the original description of FAS[27]: short palpebral fissures; smooth philtrum; and thin upper lip vermilion. Growth impairment is required, as is at least one indicator of abnormal brain development. Brain anomalies must be associated with measureable neurocognitive or neurobehavioral deficits (see criteria in[1]). The CoFASP criteria are a modification of the original and revised IOM criteria[1], which have been utilized in a substantial body of clinical and research literature. A requirement for neurobehavioral impairment was added because this domain contributes most to functional impairment and is the most important target for intervention. By consensus, CoFASP selected a liberal threshold of 1·5 standard deviations below the mean for standardized measures of neurocognition and behavior, which includes some individuals with measureable, but mild, functional deficits. Other systems require 2·0 standard deviation impairments.

As Table 1 shows, pFAS requires a history of PAE, craniofacial features, and neurocognitive / behavioral impairment. Alternatively, pFAS classification can occur without a history of PAE when craniofacial features, neurocognitive / behavioral impairment, and either growth deficiency or abnormal brain development are present. ARND (usually “neurodevelopmental disorder” or “newborn affected by maternal use of alcohol”; ICD10 F88 or P04.3) requires PAE and neurocognitive / behavioral dysfunction, but not craniofacial features or growth deficiency. Because ARND has the least stringent and least specific criteria of the FASD classifications, it accounts for a substantial proportion of the population.[2] Finally, ARBD is an infrequent diagnosis made when there is a history of PAE and a specific major malformation known to be associated with PAE in animal or human studies (e.g. cardiovascular system, skeletal system).

Neurobehavioral Disorder associated with PAE (ND-PAE) is a proposed diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) for individuals with PAE and dysfunction in three symptom domains: neurocognitive; self-regulation; and adaptive functioning.[73] Currently, ND-PAE is classified in the DSM-5 as a “condition for further study”. A significant challenge for the adoption of ND-PAE is the lack of consensus on a specific threshold for PAE (minimum level of PAE at which adverse effects are seen) and level of cognitive impairment.[73] In addition, the frequency of impairments in all three symptom domains is unknown. Finally, adaptive functioning has been less-extensively studied in FASD and may be strongly associated with potentially confounding factors such as poverty, abuse, neglect, and low socioeconomic status. Nonetheless, a direct comparison of ND-PAE criteria to a set of ARND diagnostic criteria in a clinic-referred sample found agreement of 85.7% to 94.6% and suggested the practical clinical utility of both approaches.[74] Presently, clinicians can diagnose 315.8 / F88: Other Specified Neurodevelopmental Disorder and add “associated with prenatal alcohol exposure.”

Diagnosing FASD in children and adults plays a critical role in identifying co-morbid and co-occurring conditions and accessing vocational support, housing and financial assistance, psychological interventions, and specialized legal counseling. These services may attenuate

the impact of commonly co-occurring disabilities, including academic failure, social problems, criminal behavior, alcohol and drug use disorders, and employment difficulties. Panel #2 describes the diagnosis of a child with pFAS for illustration.

Pathophysiology

Alcohol equilibrates freely from maternal to fetal circulation, disrupting maternal, placental, and fetal physiology.[75] In animal models, the outcome of these interactions is determined in part by the dose, pattern, and timing of PAE.[5] In rodents, alcohol exposure during gastrulation (approximately equivalent to day 17 of human gestation) may produce the cardinal craniofacial features of FAS, whereas exposure during neurulation (approximately the third to fourth weeks of gestation) may produce facial abnormalities more typical of DiGeorge Syndrome, a genetic condition with phenotypic features sometimes observed in FASD. PAE following organogenesis has considerably less impact on craniofacial development but continues to disrupt brain development throughout pregnancy. Hence, the most common manifestation of FASD (ARND) includes significant neurocognitive and behavioral abnormalities but lacks defining facial dysmorphology.

Alcohol disrupts development through diverse genetic, epigenetic, molecular, cellular, and physiological actions that alter the complex choreography of development across the lifespan.[76] Exposure to alcohol during gastrulation may cause FAS; however, in many instances, alcohol exposure occurs repeatedly during gestation, producing a complex set of insults to different developmental processes. Alcohol metabolism produces oxidative injury as well as toxic metabolites, such as acetaldehyde, and in animal models, antioxidants can mitigate alcohol teratogenesis.[77] Apoptotic death and impaired migration of neural crest cells leads to brain and craniofacial malformations[78] whereas death and impaired proliferation of neural stem cells likely contributes to microencephaly by shrinking the pool of neural progenitor cells.[50,79] Death of proopiomelanocortin neurons in the arcuate nucleus of the hypothalamus reduces endorphin inhibition of the hypothalamic-pituitary adrenal axis, predisposing to stress and altered circadian rhythms.[50] Alcohol-induced endocrine dysfunction, disruption of morphogen signaling, and activation of neuroinflammation all impact the developing brain and have long-term effects on immune and endocrine systems.[76,80–83] Alcohol disrupts neural cell migration and axonal pathfinding by blocking cell adhesion and axon outgrowth mediated by the L1 neural cell adhesion molecule.[84] Of note, mutations in the human L1 gene cause dysgenesis of the corpus callosum, hydrocephalus, and cerebellar dysplasia, mirroring some of the neuropathological abnormalities of FAS. Alcohol also alters craniofacial and brain development by disrupting *PDGFRA* and its downstream signaling elements, PI3K and mTOR.[85] Genetic polymorphisms in *PDGFRA* and in genes that regulate L1 sensitivity to ethanol are associated with craniofacial and brain dysmorphology in humans.[84,85]

Developmental Course

FASD has not been well studied in adults and the phenotype is older adults is unknown. Some adults received their diagnoses during childhood; however, the high prevalence of FASD and high rates of misdiagnosis in children[10] suggest that FASD is often undiagnosed

in adults. Among those diagnosed as children, the cardinal facial features of FAS are often evident in adulthood, although maturation renders some facial features subtle or absent.[4,86] Weight normalizes during development for some individuals with FASD, but short stature, microcephaly, cognitive deficits, and neurobehavioral abnormalities often persist into adulthood.[4] Reviews of adult FASD assessment and diagnosis in Canada highlighted serious gaps in services for adults compared to children and identified diverse service needs for adults: comprehensive assessment; substance-abuse screening and treatment; psychotherapy; suicide prevention; employment assistance; housing assistance; and family/parenting support.[87] Similar gaps exist in the US and other countries.

Management

Interventions for FASD tend to be multi-faceted and generally follow recommendations for other developmental disorders in children and adults, including provision of supports, accommodations, and therapies.[73] There are no specific drug treatments for FASD, and clinicians often use combinations of medications for ADHD, disorders of impulse control, aggression, and mood disorders. Two small studies (reviewed in[88]) suggest that stimulants may be effective at treating hyperactivity in FASD, despite not fully addressing inattention and impulsivity. A specialized educational intervention for math learning disability associated with FASD (also reviewed in[88]) has proven beneficial. Animal studies and preliminary studies in humans have shown some promise for choline following PAE.[89–91] A recent meta-analysis of interventions for gross motor deficits in neurodevelopmental disorders suggested some utility, but there have been very few high quality clinical trials.[92]

Conclusion and future directions

FASD represents a global public health problem that remains under-recognized and under-diagnosed despite its high prevalence and cost to society.[3,4,10] PAE is a common teratogenic event that leads to sentinel craniofacial abnormalities in a small percentage of cases[1,27] and a wide range of neuropathological abnormalities and associated cognitive, behavioral, and social impairments for many children and adults.[4,34,35,45] Social stigma, lack of awareness, and low capacity for screening and diagnosis result in the under-diagnosis of affected children and only rare diagnosis in adults.[26] Multiple diagnostic systems and disagreement over thresholds of PAE at which adverse effects occur contribute to wide variation in diagnosis and case identification around the world.[69,93] An internationally accepted consensus diagnostic system is desperately needed to advance research and clinical care globally.

Awareness of the diverse presentations of FASD will enable neurologists to assist patients and families through education, assessment of comorbidities, and referrals.[18,19,27] The introduction of web- and app-based automated tools will enhance and broaden the diagnosis and treatment of FASD. 3D imaging is already capable of identifying subtle facial features that distinguish children with heavy PAE from controls with 97% specificity for FAS and 90% for pFAS[94]. Because face and brain development are highly linked[5], it is not surprising that the detection of subtle facial dysmorphology is predictive of neurocognitive impairment, even in children without cardinal facial features of FAS or pFAS. Similarly, scalable tools

using 2D facial images can distinguish children with ARND from non-exposed children, potentially facilitating future high throughput FASD screening.[95] These tools may eventually allow the detection of craniofacial and neurodevelopmental abnormalities caused by lower levels of PAE[96], perhaps one day decreasing dependence on a documented history of PAE or the skills of dysmorphologists in the diagnosis of FASD.

Diagnosis without available treatment has limited utility[86,87]; hence, with increased diagnostic capacity, semi-automated and automated interventions will become essential. Computerized cognitive training, an increasingly common intervention for neurocognitive deficits, improves attention and working memory in children with FASD[97] and represent just one potentially scalable modality for the treatment of FASD.

Panel #1: "Is there a safe amount of prenatal alcohol exposure?"

There is general agreement among Public Health agencies and professional organizations around the world that no amount of alcohol consumption is safe during pregnancy.[16] The World Health Organization advises clinicians to ask women about alcohol use at every visit and to advise against use during pregnancy.[98] The U.K.'s Royal College of Obstetricians and Gynaecologists advises that "the safest approach is not to drink alcohol at all if you are pregnant" (RCOG Patient's Information Committee, 2018). The Australian National Health and Medical Research Council guidelines have evolved in the last decade to the current recommendation of no alcohol while pregnant or trying to become pregnant.[99] The American Academy of Pediatrics advises that there is no safe amount or type of alcohol that is safe during pregnancy nor is there a period of pregnancy during which alcohol consumption is safe.[100]

Panel 2: Case study – multi-disciplinary evaluation of a child with prenatal alcohol exposure

A 7 year old adopted boy was referred to an FASD Clinic. Exposures included first trimester binge drinking, tobacco, and marijuana. Height and weight are above the 50th percentile and head circumference is normal. He has small palpebral fissures, thin upper lip, smooth philtrum, midface hypoplasia and a diagnosis of pFAS. Cognitive testing shows borderline intelligence quotient of 75 and impairment in attention, executive functioning, and fine motor skill. He has hyperactivity, aggression, and learning deficits. He takes no medications. Parents report insomnia, frequent waking, and past night terrors. His neurological exam is unremarkable, but EEG shows diffuse slowing. MRI reveals modest thinning in the posterior corpus callosum and a single focal peri-ventricular heterotopia. The consultation yields a trial of low dose stimulant medication, a sleep study referral, and plans to collect behavior ratings on medication and to re-test attention at follow-up.

Search strategy and selection criteria

We searched PubMed and the Cochrane Library (from 2000 to December 15, 2018) using the terms "fetal alcohol syndrome", "fetal alcohol spectrum disorder", "alcohol-related neurodevelopmental disorder", and "prenatal alcohol". Further material was gathered from reference lists, review articles, the authors' own published research, and textbooks. We did

not include abstracts and reports from conferences. The final reference list was generated based on the relevance of the resulting papers to the topics covered in this review. As this is a narrative review and not a meta-analysis, we acknowledge that there is potential for bias in the topics chosen for presentation here and in the articles chosen for inclusion.

Abbreviations:

ARND	Alcohol-Related Neurodevelopmental Disorder
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorders
pFAS	partial Fetal Alcohol Syndrome

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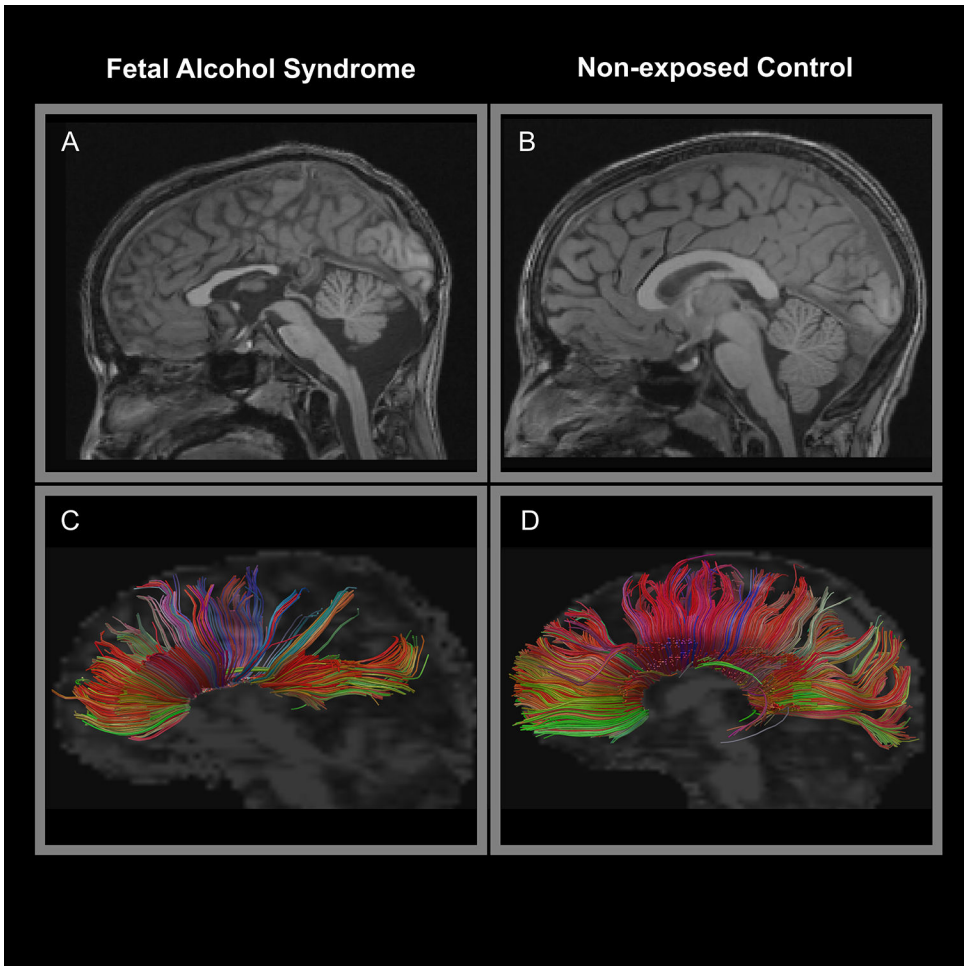

Figure 1.

Magnetic Resonance Imaging (MRI) of 12-year old males with fetal alcohol syndrome (FAS) and with typical development. T1-weighted anatomical images (A, B) show multiple abnormalities in the child with FAS, including microcephaly, partial agenesis of the corpus callosum, and cerebellar and brainstem dysplasia. Diffusion Tensor Imaging (DTI) tractography (C, D) accentuates the inter-hemispheric white matter abnormality, especially in the posterior region, in the child with FAS.

Table 1.

CoFASP Diagnostic Criteria for FASD, adopted from Hoyme et al.[1]

Diagnosis	Confirmed Prenatal Alcohol Exposure?	Dysmorphic Face	Growth Deficiency	Brain Abnormality	Cognitive or Behavioral Impairment	Other Systemic Malformation
FAS	Yes	Required	Required	Required	Required	Not required
	No	Required	Required	Required	Required	Not required
Partial FAS	Yes	Required	Not required	Not required	Required	Not required
	No	Required	Required if Brain Abnormality not present	Required if Growth Deficiency not present	Required	Not required
ARND	Yes	Not required	Not required	Not required	Required*	Not required
ARBD	Yes	NA	NA	NA	NA	Required

Confirmed prenatal alcohol exposure: ≥6 drinks/week for 2 weeks; or ≥3 drinks on ≥2 occasions; or documentation of maternal intoxication in records; or positive biomarker for alcohol; or evidence of risky maternal drinking on validated screening tool (maternal report includes the pregnancy itself AND the period up to 3 months prior to pregnancy awareness)

Dysmorphic face: ≥2 of the following: short palpebral fissures (≤10th centile); thin vermillion border; and smooth philtrum (ranked 4 or 5 on lip/philtrum guide)[66]

Growth deficiency: Height and/or weight ≤10th centile based on racially/ethnically normed charts

Brain Abnormality: Head circumference ≤10th centile, or structural brain anomaly, or recurrent non-febrile seizures;

Cognitive Impairment: Global cognitive impairment or impaired performance, verbal or spatial IQ, or individual neurocognitive domain (memory, executive function, etc.) ≥ 1.5 SD below mean;

Behavioral Impairment: Impairment of self-regulation ≥ 1.5 SD below mean; * ARND requires two behavioral or cognitive deficits if IQ is not ≥ 1.5 SD below the mean; NOTE: for children under age three, developmental delay is required.